REMARKS

Introductory Comments:

Claims 3, 6-16, 19 and 22-32 were examined in the Office Action under reply. Claims 6, 15, 16, 22, 31 and 32 were indicated as allowable if rewritten to include the recitations from the base claims from which they depend. Claims 3, 7-14, 19 and 23-30 were rejected under (1) 35 U.S.C. §103(a); and (2) the judicially created doctrine of obviousness-type double patenting. These rejections are respectfully traversed as discussed more fully below.

Applicants note with appreciation the withdrawal of the previous rejections under 35 U.S.C. §112, second paragraph and 35 U.S.C. §103(a).

The Restriction Requirement:

New claims 33 and 34, added in the previous response, have been withdrawn as directed to "an invention that is independent or distinct from the invention originally claimed." Applicants respectfully traverse this restriction. In particular, claims 33 and 34 pertain to particular MEFAs for use in the claimed methods. The Examiner alleges these claims "do not include all the limitations of previously searched subject matter deemed allowable and thus are beyond the scope of that which was previously searched." Office Action, page 2. However, at least original claims 1-3, 10, 13, 14, 17-19, 22, 26, 27, 29 and 30 read on the MEFAs recited in claims 33 and 34. Hence, a search of the original claims would have surely turned up art directed to the MEFAs recited in new claims 33 and 34.

MPEP 803 states:

> If the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to distinct or independent inventions. (Emphasis added).

Applicants submit that an examination of claims 33 and 34 along with those pending in the application would not impose a serious burden on the Examiner. Indeed, applicants believe failure to examine the claims as suggested would pose a far greater burden on the Patent and Trademark Office by requiring a duplication of effort and resources. Accordingly, reconsideration of the present restriction requirement is respectfully requested.

Overview of the Above Amendments:

The specification has been amended at page 32 to correct an obvious punctuation error.

Claims 3 and 19 have been amended to recite that in addition to the epitope from the NS3/4a region, the MEFAs comprise "a consensus sequence from the E2 hypervariable region spanning amino acids 390-410, numbered relative to the HCV-1 polyprotein sequence." Support for this amendment can be found throughout the specification as filed at, e.g., page 32, lines 7-12.

The foregoing amendments are made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to file one or more continuing applications containing the cancelled and/or unamended claims.

The amended claims are believed to place the application in condition for allowance and do not present issues that would require a new search, as a search directed to MEFAs used in the previously claimed methods would have turned up art directed to a MEFA comprising an E2 consensus sequence as now present in the claims. Accordingly, entry of the above amendments is respectfully requested.

Rejections Over the Art:

A. Claims 3, 7, 8, 10-14, 19, 23, 24 and 26-30 were rejected under 35 U.S.C. §103(a) as unpatentable over Chien et al., *J. Clin. Microbiol.* (1999) 37:1393-1397 ("Chien-1") in view of U.S. Patent No. 6,306,579 to Seidel et al. ("Seidel") and Choo et al., *Proc. Natl. Acad. Sci. USA* (1991) 88:2451-2455 ("Choo"). Chien is said "to teach a method of detecting hepatitis C virus infection in a biological sample using a MEFA containing all of the major immunogenic epitopes of HCV where the MEFA comprises at least one epitope in common with the antigen used in the solid support." Office Action, page 5. The Office notes Chien "does not provide the particular sequence of his antigen across the NS3/4a region." Office Action, page 5. However, Seidel is cited for allegedly teaching "a double antigen bridge test using HCV antigens from the NS3 region in immunological tests." Office Action, page 5. Finally, the Office asserts "Choo's

sequence is 99.5% identical to Applicant's SEQ ID NO. 2." Office Action, page 6. (SEQ ID NO:2 is the NS3/4a reference sequence recited in the claims.) The Office concludes:

> One of ordinary skill in the art would have been motivated to combine the teachings of Chien with those of the '579 patent to create an immunological test for the detection of HCV-specific antibodies using a MEFA in a double antigen bridge format because the '579 patent et al indicates that the double antigen bridge format results in increased specificity and sensitivity. Moreover, at 99.5% identity, Choo's published sequence falls squarely within Applicant's parameters of 80% sequence identity to the contiguous amino acid sequence of SEQ ID NO:2.

Office Action, page 6. However, applicants submit the combination of Chien-1 in view of Siedel and Choo does not render the present claims obvious.

To support an obviousness rejection under 35 U.S.C. §103, "all the claim limitations must be taught or suggested by the prior art." MPEP §2143.03. In addition, "the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure." MPEP §706.02; *In re Vaeck,* 20 USPQ2d 1438 (Fed. Cir. 1991). Applicants submit that the cited references do not disclose or suggest all the limitations of the present invention. Thus, a *prima facie* case of obviousness has not been presented by the Office.

Chien-1 teaches a chimeric HCV polypeptide termed "MEFA-6." As shown in Figure 1 of Chien-1, MEFA-6 includes several HCV epitopes. However, MEFA-6 does not contain a consensus sequence from the E2 hypervariable region spanning amino acids 390-410 as claimed. Rather, the E2 epitope present in MEFA-6 includes the amino acid sequence found at positions 405-444 of HCV-1. There is no teaching or suggestion to provide a multiple epitope fusion antigen as claimed, that includes a consensus sequence from the E2 hypervariable region. The inclusion of such a sequence allows the detection of various HCV-1 isolates, thus increasing the sensitivity of the assay.

Seidel and Choo do not fill the missing gaps. Neither of these references even hints at the use of any kind of an HCV MEFA, let alone a MEFA with a consensus sequence from the E2 hypervariable region. Seidel therefore completely fails to teach or suggest the use of **both** a MEFA and an NS3/4a antigen in an assay as claimed in the current application. For its part, Choo provides the sequence of the HCV-1 polyprotein. The polyprotein described in Choo

includes over 3000 amino acids. Although Choo's full-length sequence includes an internal sequence with homology to the NS3/4a epitope used in the claimed assays, there is absolutely no suggestion in Choo to use this or any other particular portion of the polyprotein in immunoassays as claimed. In fact, the last sentence on page 2454 of Choo explains "the identities of the individual HCV proteins have not yet been established." Thus, Choo provides absolutely no guidance with respect to the use of an NS3/4a epitope and certainly provides no suggestion or motivation to use this particular epitope, unidentified by Choo, in assays with an NS3/4a antigen as claimed.

Based on the foregoing, applicants submit the cited combination fails to render the instant claims obvious and withdrawal of this basis for rejection is respectfully requested.

B. Claims 9 and 25 were rejected under 35 U.S.C. §103(a) as being unpatentable over Chien-1 in view of Seidel and Choo, and further in view of Chien et al., *Proc. Natl. Acad. Sci. USA* (1992) 89:10011-10015 ("Chien-2"). Claims 9 and 25 are directed to an assay method using a MEFA with the full-length helicase region of NS3, spanning amino acids 1193-1657. The Office applies Chien-1, Seidel and Choo as above. With respect to Chien-2 the Examiner argues:

> Figure 1 of Chien et al. (1992) on page 10012 indicates that the C33C polypeptide which was part of Chien's C25 chimeric polypeptide is derived from the NS3 region. Also on page 10012 Chien indicates that '[t]he C33C polypeptide...is derived from most of the NS3 region that appears to encode both a viral protease and a helicase'....It is not clear from the disclosure whether Chien included the entire helicase region in his MEFA, as currently claimed by applicant, but the statement certainly strongly suggests its inclusion.

Office Action, page 7. However, applicants respectfully disagree with this assessment.

As explained above, the combination of Chien-1 in view of Seidel and Choo is not believed to render the base claims from which claims 9 and 25 depend obvious. The addition of Chien-2 to the combination does not cure the defects of the primary and secondary references. In particular, the Office's assessment of Chien-2 is in error. As explained on page 10011, at line 8 of the Materials and Methods section, the C33C antigen used in Chien's C25 chimeric antigen included only 266 amino acids. The full-length helicase domain spanning amino acids 1193-1657 as claimed in claims 9 and 25, on the other hand, includes 465 amino acids, and is therefore

almost 200 amino acids longer! Moreover, there is no indication in Chien-2 regarding just which 266 amino acids of NS3 were used. Accordingly, there is absolutely no teaching or suggestion in Chien-2 of a MEFA containing the full-length helicase region of NS3, spanning amino acids 1193-1657, and the use of such a MEFA in assays as claimed. Thus, this basis for rejection should also be withdrawn.

C. Claims 3, 7, 8, 10-14, 19, 23, 24, and 26-30 were rejected under 35 U.S.C. §103(a) as unpatentable over U.S. Patent No. 6,428,792 to Valenzuela et al. ("Valenzuela") in view of Seidel and Choo. The Office argues Valenzuela teaches MEFA-3, MEFA-5 and MEFA-6 that include "epitopes from the NS3(protease)/NS4a(helicase) region." Office Action, page 8. Seidel is cited for teaching a double antigen bridge test and Choo is said to teach a sequence 99.5% identical to SEQ ID NO:2. However, as with those combinations above, the present combination is not believed to render the claims obvious.

In particular, as noted by the Office, Valenzuela fails to describe a double antigen bridge assay method. Moreover, Valenzuela does not speak to the use of a conformational epitope of NS3/4a. Similarly, Seidel completely fails to teach or suggest the use of any MEFA, let alone the particular MEFAs used in the claimed assays and certainly does not teach the use of **both** a MEFA and an NS3/4a antigen in an assay. As with Seidel, Choo fails to describe an assay as claimed, using both a MEFA and an NS3/4a antigen. To reiterate, the polyprotein described in Choo includes over 3000 amino acids and there is no suggestion or teaching as to the boundaries of particular HCV regions of the polyprotein, such as the NS3/4a region, now known to be present in the polyprotein. Moreover, Choo on its face states that the identities of the various regions had not yet been determined. Therefore, Choo fails to provide any guidance with respect to the use of an NS3/4a epitope and provides no suggestion or motivation to use this particular unidentified epitope in assays with an NS3/4a antigen as claimed.

Without a suggestion to modify the teachings of the cited art evident therein, the only conclusion supported by the record, should the rejection be maintained, is that the rejection was made impermissibly using hindsight reconstruction of the invention. As stated by the Court of Appeals for the Federal Circuit, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the

claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). See, also, *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988): "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."

Based on the foregoing, applicants respectfully request the withdrawal of the rejection of claims 3, 7, 8, 10-14, 19, 23, 24, and 26-30 over the combination of Valenzuela in view of Seidel and Choo.

D. Claims 9 and 25 were rejected under 35 U.S.C. §103(a) as being unpatentable over Valenzuela in view of Seidel and Choo, and further in view of Chien-2. The combination of Valenzuela in view of Seidel and Choo is applied as in the combination described immediately above in section C. Applicants have explained why this combination is inapplicable to the base claims from which claims 9 and 25 depend. Chien-2 is applied as in section B above. In particular, Chien-2 is cited for purportedly suggesting the helicase domain sequence recited in claims 9 and 25. To reiterate, page 10011, line 8 of the Materials and Methods section of Chien-2 explains the C33C antigen used in the C25 chimeric antigen included only 266 amino acids. The helicase domain recited in claims 9 and 25, on the other hand, spans amino acids 1193-1657 and therefore includes 465 amino acids, almost 200 amino acids more than the portion of the helicase domain used in Chien-2. Additionally, Chien-2 does not explain which 266 amino acids of NS3 were used. Contrary to the Office's assertion then, there is no teaching or suggestion in Chien-2 of a MEFA containing the full-length helicase region of NS3, spanning amino acids 1193-1657, and the use of such a MEFA in assays as claimed.

Again, this rejection appears to be premised on hindsight reconstruction using applicants' claims as a template to piece together the teachings of the cited art. This the Office cannot do. Thus, withdrawal of this basis for rejection is respectfully requested.

E. Claims 3, 7-14, 19 and 23-30 were rejected under 35 U.S.C. §103(a) as being unpatentable over Chien-2 in view of Seidel and Choo. Chien-2 is alleged to teach an immunodominant chimeric polyprotein (termed "C25" therein) using regions from NS3, NS4

and core of HCV. The Office reiterates its assertion that Chien-2 appears to be using the entire helicase region. The Office correctly notes Chien does not describe a double antigen bridge test. Seidel is again cited for allegedly teaching such an assay using HCV antigens from the NS3 region and Choo is cited for allegedly teaching a sequence 99.5% identical to applicants' SEQ ID NO. 2 (SEQ ID NO:2 is the NS3/4a reference sequence recited in the claims.) The Office concludes:

> One of ordinary skill in the art would have been motivated to combine the teachings of Chien with those of Seidel to create an immunological test for the detection of HCV-specific antibodies using a MEFA in a double antigen bridge format because Seidel et al indicates that the double antigen bridge format results in increased specificity and sensitivity.

Office Action, page 12. However, applicants submit the combination of Chien-2 in view of Siedel and Choo does not render the present claims obvious.

As shown in Figure 1 of Chien-2, the HCV sequences present in the C25 chimeric polypeptide consist of an epitope from NS3, an epitope from NS4 and an epitope from core. C25 does not contain an epitope from E2, and certainly does not teach or suggest the use of a consensus sequence from the E2 hypervariable region spanning amino acids 390-410 as claimed. Additionally, there is no disclosure of the NS3/4a sequence of SEQ ID NO:2. Seidel also fails to teach these elements of the claims. As explained above, Choo only pertains to the full-length HCV polyprotein and does not delineate regions of the protein, let alone regions that might be useful for use in assays as claimed. Again, it is evident the Office is engaging in improper hindsight reconstruction in making this rejection. Withdrawal of this basis for rejection is therefore respectfully requested.

The Obviousness-type Double Patenting Rejections:

The claims have been variously rejected under the judicially created doctrine of obviousness-type double patenting over U.S. Patent Nos. 6,428,792; 6,632,601; 6,797,809; 6,630,298; and U.S. Application Nos. 10/643,853; 10/174,652; and 10/899,716.[1]

[1] Applicants assume the Office intended to reject the claims over U.S. Application No. 10/899,715, not 10/899,716 as they are unaware of an application corresponding to 10/899,716.

Applicants are submitting a terminal disclaimer over the '601 and '298 patents. However, the rejections over the '792 and '809 patents, as well as over U.S. Application Nos. 10/643,853, 10/174,652 and 10/899,715, are respectfully traversed for the reasons provided below.

In particular, claims 3, 6-16, 19 and 22-32 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-58 of copending U.S. Application No. 10/643,853. Applicants traverse.

The claims currently pending in the '853 application (claims 47-58) are all directed to polynucleotides, vectors, host cells and methods of recombinant production. The claims **do not** pertain to immunoassays as claimed in the instant application. Applicants submit that polynucleotides and immunoassays are separately patentable inventions and that a terminal disclaimer is not necessary. In fact, the '853 application is a divisional of U.S. Application No. 09/881,239, the application that ultimately issued as U.S. Patent No. 6,630,298, cited above. The '239 application was filed to pursue polynucleotide claims that had been restricted from the immunoassay method claims. More specifically, there was a three-way restriction requirement (dated June 11, 2002) in the '239 application that named three groups of claims -- Group I, claims 1-43, drawn to a solid support with bound antigens, kit, method of use in immunoassays and method of making; Group II, claims 44-46, drawn to a fusion antigen; and Group III, claims 47-58, drawn to a polynucleotide, vector, host cell and method of making a protein. Thus, the Patent Office itself recognizes that polynucleotides, vectors, host cells and methods of recombinant production are separate and distinct from immunoassay methods. Since immunoassay methods constitute a separately patentable invention, applicants respectfully request withdrawal of the obviousness-type double patenting rejection over the '853 application.

Additionally, claims 3, 6-16, 19 and 22-32 were rejected under the judicially created doctrine of obviousness-type double patenting over claims 29-47 of U.S. Application No. 10/899,715. However, as with the obviousness-type double patenting rejection discussed above, all of the claims of the '715 application pertain to polynucleotides, vectors, host cells and methods of recombinant production. These claims were considered patentably distinct from immunoassay methods in the original parent application (U.S. Application No. 09/881,654) from which U.S. Patent No. 6,632,601, cited above, derived. In particular, there was a three-way restriction requirement (dated June 11, 2002) in the '654 application as follows: Group I, claims

1-24, drawn to a solid support, kit, methods of use and methods of making; Group II, claims 25-28, drawn to a fusion antigen; and Group III, claims 29-47, drawn to a polynucleotide, vector, host cell and methods of recombinant production. Accordingly, as with the obviousness-type double patenting rejection above, the present rejection is inappropriate as claims 29-47 were considered to be separately patentable from immunoassay methods. Withdrawal of the rejection over the '715 application is therefore respectfully requested.

Claims 3, 6-16, 19 and 22-32 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-49 of copending U.S. Application No. 10/174,652. Applicants request this rejection be held in abeyance until allowable subject matter is indicated in either or both of the instant application and/or the '652 application. Applicants will then consider the propriety of filing a terminal disclaimer vis-a-vis the allowed claims.

Claims 3, 6-16, 19 and 22-32 were also rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-20 of U.S. Patent No. 6,428,792 and claims 1-4 of U.S. Patent No. 6,797,809. Applicants respectfully traverse these rejections.

Claims 1-20 of the '792 patent and claims 1-4 of the '809 patent are directed to MEFAs *per se* not to immunodiagnostic methods. As demonstrated above, the Patent Office views MEFAs and immunodiagnostic methods as separately patentable inventions. Indeed, as with the '853 application above, the '809 patent was filed as a divisional application off of parent Application No. 09/881,654, the application that ultimately issued as U.S. Patent No. 6,632,601. There was a three-way restriction requirement in the '654 application as follows: Group I, claims 1-24, drawn to a solid support with bound antigens, kit, method of use in immunoassays and method of making; Group II, claims 25-28, drawn to a fusion antigen; and Group III, claims 29-47, drawn to a polynucleotide, vector host cell and method of making a protein. Thus, as with the application described above, the Patent Office recognized that MEFAs and methods of using the MEFAs in immunoassays were patentably distinct. Accordingly terminal disclaimers over the '792 and '809 patents should not be required and withdrawal of these bases for rejection is respectfully requested.

CONCLUSION

Applicants respectfully submit that the claims define a patentable invention. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

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